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DISCOvERIE

Development, dIagnostic and prevention of gender-related Somatic and mental COmorbitiEs in iRritable bowel syndrome In Europe

Workpackage 2
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Report on IBS pattern comorbidities in retrospective cohorts

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List of Abbreviations

GI	Gastrointestinal
IBS	Irritable Bowel Sydrome
CFS	Chronic Fatigue Syndrome
HAD	Hospital and Depression Scale
GAD7	Genarlised Anxiety Disorder 7-item scale
PHQ	Patient Health Questionnaire
IBS-SSS	IBS- Symptom Severity Scale
GSRS	Gastrointestinal Symptom Rating Scale
FIQ	Fibromyalgia Impact Questionnaire
WP	Work Package

Executive summary

Background

Psychological distress has previously been shown to affect gastrointestinal (GI) symptom severity negatively and reduce quality of life among patients with irritable bowel syndrome (IBS). However, somatic co-morbidities, such as fibromyalgia and chronic fatigue syndrome have also been reported to have impact on both mental and physical quality of life in IBS. Establishing the impact of somatic and mental co-morbidities in a large cohort is warranted.

Aim

The aim of this report is to present the work done the last months as part of the Grant Agreement. We aimed to estimate the prevalence of psychological distress (anxiety and depression), fibromyalgia and chronic fatigue syndrome (CFS) in existing IBS cohorts from different centers in the DISCOvERIE consortium, and the impact on GI symptoms and quality of life. Furthermore, we aimed to investigate prevalence of GI symptoms in primarily psychiatric populations and the background population based on data from the Hungarian National Database.

Methods

The cohorts from seven centers were received for consideration. Cohorts presented with an IBS diagnosis, a measure of GI symptom severity, and questionnaires or a doctor's diagnosis assessing psychological distress and somatic symptoms were included in the analysis. Validated cut-off levels for anxiety and depression from questionnaires or a doctor's diagnosis were used to assess presence of psychological distress. When presence or absence of a diagnosis of somatic comorbidities were unavailable, proxy markers for fibromyalgia/ widespread bodily pain and chronic / severe fatigue were used from validated questionnaires. Prevalence of anxiety, depression, fibromyalgia / widespread bodily pain and chronic / severe fatigue, and the GI symptom severity were presented. Comparisons of demographic information, GI symptom severity, and quality of life between subjects with/without comorbidities were performed with Students t-test. As different questionnaires were used to assess GI symptom severity and quality of life, these scores were standardized using z-scores in cohorts including at least 100 subjects. Finally, combined analyses

of all cohorts using z-scores and linear contrast analyses to determine the cumulative effect of number of mental and somatic comorbidities on GI symptom severity and quality of life were done in a pooled cohort from the different centers.

Results

Anxiety, depression, fibromyalgia / widespread bodily pain and chronic / severe fatigue were common in all the different cohorts. The cohort from Bologna was limited to 18 subjects and with limited information on comorbid conditions and therefore not included in further analyses. Patients with comorbid conditions tended to be younger and were more commonly females. Overall GI symptom severity was higher and quality of life lower, among patients with anxiety, depression or both in all cohorts except for one, and a similar pattern was seen for patients with vs. without somatic comorbidities. After standardization of GI symptom severity and quality of life between the cohorts, analyses showed linear trends with a significant increase in GI symptom severity and reduction in quality of life with increasing number of comorbidities.

Conclusion

Psychological distress and somatic comorbidities are common among patients with IBS and associated with increased GI symptom severity and reduced quality of life. Due to limitations caused by the COVID-19 crisis, analyses of cohorts including patients with primary psychiatric diagnosis focusing on presence of GI symptoms in these patients have not yet been analyzed. Direct comparison of the data generated from the IBS cohorts with the Hungarian National Database is limited by the big discrepancy between the mode of data collection and basic demographics between the populations. However, the data generated for the Hungarian National Database is of interest and may be used for hypothesis generation. A summary of the findings from the database is summarized including tables in appendix 2.

Short Introduction

Irritable bowel syndrome (IBS) is a common functional bowel disorder with a prevalence of 5-10% in the general population. The diagnostic criteria according to ROME IV is recurrent abdominal pain associated with defecation and a change in stool consistency or frequency. Gastrointestinal (GI) symptom severity varies within the patient population and demonstrate associations with severity of non-GI symptoms. A large proportion of patients with IBS report anxiety and depression, psychological distress, as well as somatic comorbidities, fibromyalgia and chronic fatigue syndrome (CFS). Previous studies have shown an increased GI symptom burden and a reduction in quality of life (QoL), among subjects with mental and somatic co-morbidities, however, the number of subjects in previous studies have been limited. We have therefore performed an investigation on existing cohorts of IBS patients at six different centers in the DISCOvERIE consortium. We have analyzed the prevalence of mental and somatic disorders, or used proxy measures hereof, and determined the impact of these factors on GI symptom severity and QoL in IBS. Furthermore, we intended to perform analysis on patients seeking health care with psychiatric disorders, with or without somatic co-morbidities, and determine the presence of IBS and the GI symptom pattern. This analysis has however not been possible, because of insufficient registration of GI symptoms in these patients. One dataset from one of the psychiatric centers in the consortium was received, but did not fulfill the criteria for inclusion in this report. We also planned to use the large Hungarian National database of diagnoses in the general population to analyze IBS and its comorbidities at the population level. The information from this big database, has now been granted to the authors of the report after some delay due to the ongoing pandemic.

Main part

Methods

We included six different cohorts from six different centers, VHIR, KUL, UNIBO, UM, UKL-HD, and UGOT for data analysis. Information regarding gastrointestinal symptoms and severity, anxiety and depression, and somatic comorbid diagnoses or questionnaires with potential proxy measures for these diagnoses / symptoms was mandatory for inclusion in further analysis. A table over the cohorts and questionnaires used can be found in appendix 1.

Questionnaires

Anxiety and Depression

Hospital and Depression Scale (HAD) is a 14-item questionnaire measuring anxiety and depression, intended to be used in non-psychiatric populations. The maximum score is 21 on the two subscales of anxiety and depression, respectively. A high score indicates a high level of psychological distress. When HAD score was available, we used validated cut-off scores on HAD subscales to categorize patients with anxiety or depression (HAD score ≥ 8). Generalized Anxiety Disorder 7-item scale (GAD7), a 7-item questionnaire validated for measuring anxiety in the general population, was used in some of the cohorts. The total score of GAD-7 ranges from 0 to 21. A validated cut off score ≥10 was used to define presence of anxiety in the cohorts where this questionnaire was used. Depression has also been evaluated using Patient Health Questionnaire 9 (PHQ-9), a 9 item questionnaire designed for use in primary care as a brief diagnostic and severity measure of depression in research and clinical practice. The sum of scores of the PHQ-9 range from 0 to 27. The same validated cut-off as for GAD-7 (≥10) was to define depression in cohorts where this questionnaire was used (moderate depression).

Gastrointestinal symptom severity

Two different questionnaires were used to assess the severity of GI symptoms; the IBS Severity Scoring System (IBS-SSS) and the Gastrointestinal Symptom Rating Scale (GSRS). IBS-SSS is a five-item questionnaire measuring frequency and intensity of GI symptoms and the interference with daily life, with total scores ranging from 0 to 500. The higher score, the more severe the symptoms. GSRS consists of 15 questions using a 7-point Likert scale. The total GSRS score is a measure of overall GI symptom severity, although it can also be divided into five GI symptom domains, but the domain scores were not used in this study.

Quality of Life

QoL was measured using three different questionnaires, two disease-specific and one generic QoL instrument. In the Gothenburg cohort, the disease-specific QoL instrument IBS Quality of Life questionnaire (IBSQOL) was used, which consists of 30 questions divided into nine domains: Emotional health, Mental health, Sleep, Energy, Physical functioning, Food/Diet, Social role, Physical role, and Sexual relations. The raw scores are transformed into scores in each of the nine scales ranging from 0 to 100, where a higher score indicates better quality of life. For the analyses

in this study, scores in the different subscales were added, divided by the number of domains, computing a mean score as a measure of overall QoL.
In the cohort from Leuven the 34-item disease-specific QOL questionnaire, IBS Quality of Life questionnaire (IBS-QOL), assessing QoL in eight domains: dysphoria, interference with activities, body image, health worry, food avoidance, social reactions, sexual health, and effect on relationships was used. Additionally an overall QOL score is frequently used for this questionnaire, and was also calculated for this cohort. The total score is presented as a percentage, where a higher score indicates better quality of life. In the cohorts from Maastricht and Heidelberg SF-36 was used to assess QoL. The SF-36, a self-report, generic health related QoL measure, includes 8 multi-item scales (35 items) that evaluate the extent to which an individual's health limits his or her physical, emotional, and social functioning: physical functioning (10 items), role limitations caused by physical health problems (4 items), role limitations caused by emotional health problems (3 items), social functioning (2 items), emotional well-being (5 items), pain (2 items), energy/fatigue (4 items), and general health perceptions (5 items). An additional item assesses change in the respondent's health over the preceding year. For the analyses in this study, we combined the different domains into one overall QoL score, ranging from 0 to 100, with higher scores indicating better QoL.

Fibromyalgia and CFS

Diagnosing fibromyalgia using a questionnaire is only possible by using the Fibromyalgia Impact Questionnaire (FIQ) from 1991. In 2010 American College of Rhematology developed preliminary diagnostic criteria for fibromyalgia, which necessitates that the patient is seen by a physician. In the cohort from Barcelona, the diagnosis of fibromyalgia was assessed by a physician, prior to inclusion. FIQ was not used in any of the cohorts. Instead, questions from PHQ-9 (assessment of depression) and PHQ-15 (a somatic symptom severity scale) have been used as proxy measures of fibromyalgia or widespread bodily pain. The questions refer to symptoms present the last four weeks. Questions b, c and e from PHQ-15 regarding back pain, pain in legs and arms and headache, have been used in combination with question d and g (regarding fatigue and cognitive impairments) from PHQ-9. This was done in order to mimic the two parts of ACR criteria (widespread pain index and somatic symptoms). The exact cut-off levels used were, (PHQ15f+PHQ9d+PHQ9g)>2 and (PHQ15b+PHQ15c)>3 for categorization as having widespread bodily pain /fibromyalgia-like symptoms. In the Maastricht cohort, where these questionnaires were not available, a question regarding presence of bodily pain on the SF-36 quality of life questionnaire was instead used to define presence of widespread bodily pain (“How much bodily pain have you had during the past 4 weeks”; “severe” or “very severe” to qualify for widespread bodily pain).
The diagnosis of chronic fatigue syndrome was assessed by a physician in the cohort from Barcelona, prior to inclusion. In the other cohorts, a formal diagnosis of chronic fatigue syndrome was not available. Instead, data from questionnaires were used to define presence of chronic or severe fatigue. In the cohorts from Leuven and Gothenburg, question four in PHQ-9, “Do you feel tired or have little energy?” was used . The question can be answered from 0 to 3, based on the frequency of symptoms. If the subjects have symptoms more than half of the days, they were categorized as having chronic or severe fatigue. In the cohort from Heidelberg, a question from PHQ-15, a somatic symptom score was used. A patient answering “bothered a lot” on the question “Do you feel tired or have low energy” was categorized as having chronic or severe fatigue. In the Maastricht cohort, where these questionnaires were not available, a question regarding presence of fatigue on the SF-36 quality of life questionnaire was used, to define presence of chronic / severe fatigue (“How much of the time Did you feel tired”; “most of the time” or “all of the time” to qualify for chronic or severe fatigue).

Statistical analysis

All statistics were performed in R (version 3.4.3-“Kite-eatingtree”). Between group comparisons regarding GI symptom severity, QoL and age between groups with vs without the different co-morbidities were performed using students t-test. Gender differences in groups with and without comorbidities were performed with Chi square test. Due to the use of different questionnaires for assessing GI symptom severity and QoL, standardization was performed using z-score. To explore the possible cumulative effect of co-morbidities on GI symptom severity and QoL, correlation analysis and one-way between-groups analysis of variance with linear contrast analysis (linear trends) were used. Investigating the effect of co-morbidities on QoL was only analyzed using total scores of QoL. Comparing prevalence of co-morbidities between groups was examined using chi-squared test or Fishers exact test. A p-value<0.05 was considered significant.

Results

2403 patients with IBS were included in the analysis, 73.6% females. The prevalence of somatic and mental comorbidities in the different cohorts is presented in Table 2, and both psychological and somatic comorbidities were found to be common. Different approaches used to categorize subjects using proxy markers from validated questionnaires may account for some of the differences found between the cohorts. Patients with comorbid conditions tended to be younger and more commonly females (Tables11.a-f). Patients with anxiety and/or depression reported more severe GI symptoms than patients without these comorbidities (Table 3a), and the same pattern was seen for patients with vs. without somatic comorbidities (Table 3b,c). Using a linear trend analysis, a gradual increase in GI symptom severity (z score) with increasing number of psychological and somatic comorbidities was seen in all cohorts combined, using groups of 0, 1, 2, and 3-4 comorbidities (N=1914, z median (IQR): (-0.19(-0.90 -0.49), 0.06(-0.64-0.71), 0.28(-0.38-0.89), 0.57(-0.25-1.18), $p<0.001$, partial η^2 =0.060) (Figure 1). A similar pattern was seen for QoL, with reduction of QoL in patients with psychological and somatic comorbidities in all individual cohorts (Tables 12a-c). When using linear trend analysis with all cohorts combined, using the same approach as for GI symptom severity , a gradual reduction in QoL was seen with increasing number of comorbidities (N=1793, z median (IQR): (0.71(0.09-1.15), 0.07(-0.60-0.59), -0.52(-0.98-0.12), -0.97(-1.55—0.29), $p<0.001$, partial η^2 =0.304) (Figure 2)

Conclusion

The prevalence of psychological distress is high in the IBS population and combined with the somatic co-morbidities fibromyalgia/ widespread bodily pain and chronic and severe fatigue, they have an impact on the GI symptom severity and QoL among IBS patients. These results support that abnormal gut-brain interactions constitute a valid pathophysiological model to explain symptom generation in a large part of the patients. The exploratory nature of the analysis performed do not make it possible to conclude the causality of co-morbidities on IBS. However, the results encourage further investigations assessing the link between the gut and the brain in depth in patients with IBS and determine the relevance for symptom generation. The major setbacks due to the COVID crisis have however had major impact in the ability to draw firm conclusions from our analyses. The control population from psychiatric centers, would definitely help address the overall magnitude and relevance of comorbidities in IBS. Although data from the Hungarian National Database have been collected and analyzed, the population differ regarding both diagnosis and age, a direct comparison with the IBS cohorts is limited. However, the consortium will address the these aspects when gathered for discussion in the near future.

Author contribution

The work of this report is a production by the DISCOvERIE Consortium. Leader of WP2, prof. Magnus Simrén has together with his staff, gathered the information from the contributing centers, performed the analysis and written the first draft of the report. Access to data in the cohorts have been granted from seven different centers, VHIR, KUL, UNIBO, UM, UKL-HD, GUF and UGOT. Data from GUF and six different cohorts from UNIBO did however not fulfill our inclusion criteria and was not included in the report.

COVID-19 crisis implication on the project

According to the detailed Grant Agreement, combined with the data presented in this report, data from the Hungarian National Database (SU;> 10 million records) was planned to be analyzed in order to compare epidemiological records of patients with IBS and its comorbidities. Hungary has however, been severely affected by the COVID-19 crisis. Previously this month, prof. István Bitter, Department of Psychiatry and Psychotherapy, Semmelweis University, Budapest, Hungary and his team have extracted data from the Hungarian National Database. Their work with data collection and analysis is summarized in Appendix 2. The last part of this report, subjects with primarily psychiatric diseases were planned to be analyzed regarding prevalence of IBS and GI symptom pattern. However, COVID-19 has had implications on the ethical committees delaying permission to access the data and transferring it to Gothenburg. Furthermore, preparation of the databases for analyses by the researchers has been delayed due to the crisis, where researchers have focused on COVID-19 related clinical work and tasks.

Appendix 1

Table 1. Questionnaires used in the different cohorts

	Bologna	Barcelona	Gothenburg	Heidelberg	Leuven	Maastricht
Questionnaires						
Rome II		X				
Rome III	X	X	X	X		X
Rome IV	X		X		X	
IBS-SSS score		X	X	X	X	
Short form 12 items Health survey (SF-12)	X					
SF-36			X	X		X
GSRS	X					X
Patient Health Questionnaire-15			X	X	X	
Likert scale (0-4) to evaluate gastrointestinal symptoms						
IBS-QoL / IBSQOL			X		X	
Profile of Mood States (POMS)						
General Anxiety Disorder-7 (GAD-7)	X		X	X	X	
Hospital Anxiety and Depression Scale (HADS)	X		X			X
MFI and FIS			X			
Patient Health Questionnaire-9 (PHQ-9)	X		X	X	X	

	Barcelona	Gothenburg	Heidelberg	Leuven	Maastricht
N	165	955	294	470	501
Subjects	IBS-D	IBS diagnosed by gastroenterologist	IBS	Patients with IBS diagnosed by GP.	IBS
Female f/m (%)	112/53 (68%/32%)	719/236 (75%/25%)	211/83 (72%/28%)	348/113 (75%/25%)	367/134 (73%/27%)
Age median (range)	35 (18-64)	35 (18-76)	38 (17-78)	39 (18-83)	45 (17-79)
Rome criteria used in diagnosis	II, III	II, III, IV	III	71% had IBS according to ROME IV	III
Symptom severity, mean ± Std	258 ± 94	304 ± 88	282 ± 101	268 ± 98	51 ± 13
Anxiety (%)	68 (42%)	409 (43%)	93 (42%)	108 (24%)	191 (38%)
Depression (%)	27 (17%)	216 (23%)	130 (45%)	113 (24%)	107 (21%)
Fibromyalgia / widespread bodily pain (%)	4 (3%)	32 (6%)	23 (8%)	38 (8%)	90 (18%)
Chronic / severe fatigue (%)	1 (1%)	105 (30%)	148 (51%)	212 (47%)	167 (33%)
Quality of life – mean score over all domains[1]	N/a	64±17	52±21	68±17	60±20

Table 2. Baseline characteristics and prevalence of comorbidities

Anxiety measured with HAD-A: Gothenburg, Maastricht; GAD7: Heidelberg, Leuven; physician diagnosis: Barcelona
Depression measured with HAD-D: Gothenburg, Maastricht; PHQ9: Heidelberg, Leuven; physician diagnosis: Barcelona
Fibromyalgia measured through a combination of PHQ15 and PHQ9 questions: Gothenburg, Heidelberg; physician diagnosis: Barcelona, Leuven; SF36 Bodily pain severe/very severe: Maastricht
Chronic / severe fatigue measured through PHQ12n=2: Heidelberg PHQ9d>1: Leuven, Gothenburg, physician diagnosis: Barcelona; SF36 vitality 4: tired all of the time/most of the time: Maastricht.
IBS severity measured with GSRS (15-item): Maastricht; IBS-SSS: Barcelona, Heidelberg, Leuven, Gothenburg.
[1] Not to be used as a valid total score due to difference in questionnaires used among the cohorts. Only for comparisons and in linear trends analysis. This score equals percent.

Table 3a. IBS severity in patients with/without psychological distress

	No anxiety or depression	Anxiety or depression	p
Barcelona	245 (89)	268 (97)	0.11
Gothenburg	288 (87)	324 (84)	<0.001
Heidelberg	250 (100)	316 (93)	<0.001
Leuven	248 (93)	310 (92)	<0.001
Maastricht	48 (13)	54 (13)	<0.001

Mean (sd) Difference between groups: t-test.

Table 3b. IBS severity in patients with/without fibromyalgia / widespread bodily pain

	No fibromyalgia / w b p	Fibromyalgia / w b p	p
Barcelona	254 (93)	322 (79)	0.18
Gothenburg	306 (85)	367 (61)	<0.001
Heidelberg	283 (99)	310 (87)	0.19
Leuven	262 (96)	320 (102)	0.002
Maastricht	49 (13)	59 (13)	<0.001

Mean (sd) Difference between groups: t-test.

Table 3c. IBS severity in patients with/without chronic or severe fatigue.

	No comorbidities	Chronic fatigue	p
Gothenburg	288 (81)	331 (85)	<0.001
Heidelberg	258 (97)	304 (101)	<0.001
Leuven	235 (95)	302 (87)	<0.001
Maastricht	48 (13)	56 (12)	<0.001

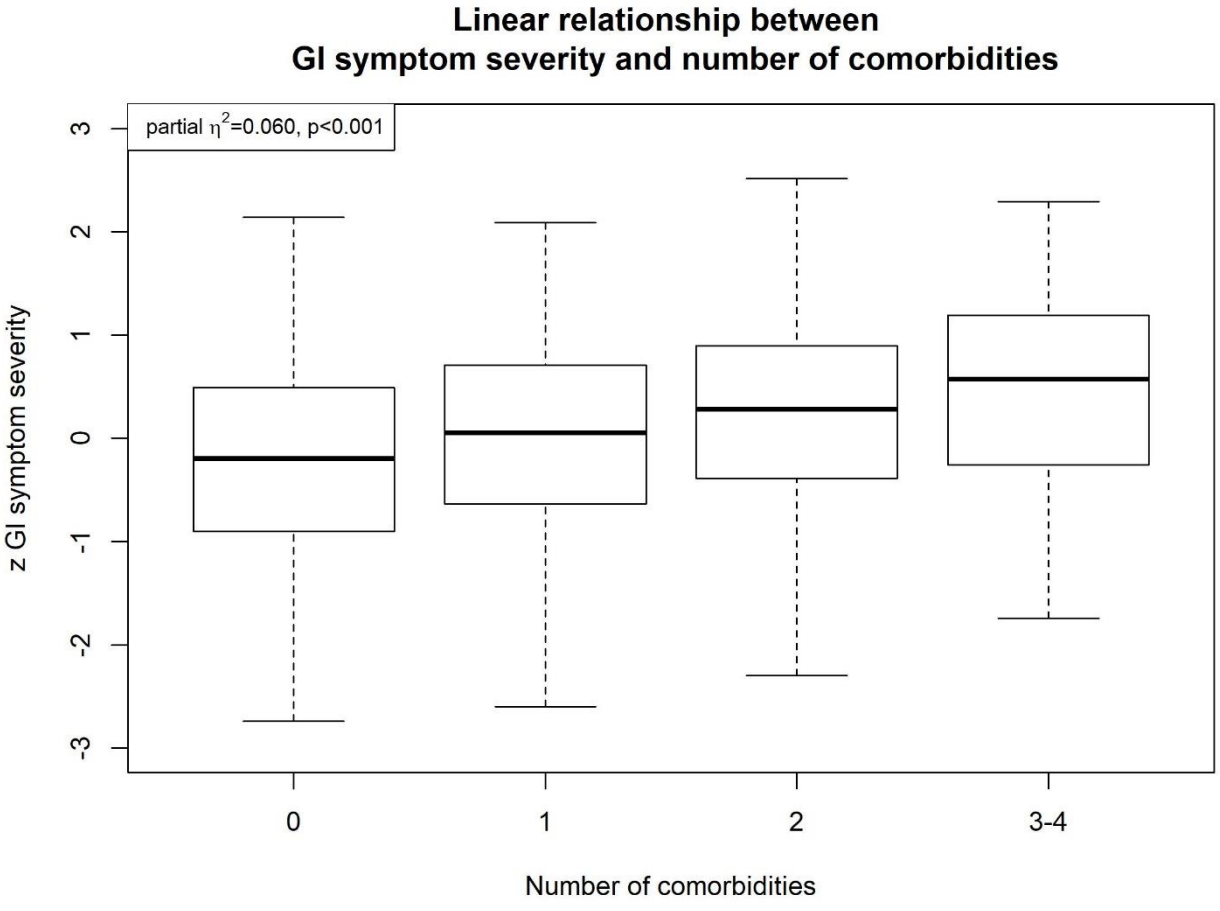
Mean (sd) Difference between groups: t-test. Barcelona cohort excluded due to n=1 with CFS.

Number of comorbidities	Median [IQR]	P-value
0	-0.37 [-1.00 - 0.33]	
1	0.11 [-0.56 - 0.72]	<0.001
2	0.37 [-0.36 - 0.93]	
3-4	0.64 [-0.16 - 1.25]	

Table 4. Linear trends merged cohort.

Linear trends (N=1914) partial eta squared: 0.10, p-value<0.001

Figure 1.



Median [IQR] and range for the ”number of comorbidity”-groups.

Table 5a Anxiety

	Gothenburg	Heidelberg	Barcelona	Leuven	Maastricht	p
No anxiety	539 (57%)	197 (68%)	93 (58%)	339 (76%)	309 (62%)	<0.001
Anxiety	409 (43%)	93 (32%)	68 (42%)	108 (24%)	191 (38%)	

Number (percentage) of patients with or without anxiety in the different cohorts, and the overall Chi squared p-value.

Table 5b Anxiety prevalence between groups

	Gothenburg	Heidelberg	Barcelona	Leuven	Maastricht
Gothenburg	-	<0.001	0.90	<0.001	0.08
Heidelberg		-	0.04	0.02	0.10
Barcelona			-	<0.001	0.41
Leuven				-	<0.001
Maastricht					-

Chi squared test p-values between two cohorts

Table 6a Depression

	Gothenburg	Heidelberg	Barcelona	Leuven	Maastricht	p
No depression	732 (77%)	162 (55%)	134 (83%)	352 (76%)	392 (79%)	<0.001
Depression	216 (23%)	130 (45%)	27 (17%)	113 (24%)	107 (21%)	

Number (percentage) of patients with or without depression in the different cohorts, and the overall Chi squared p-value.

Table 6b. Depression prevalence between groups

	Gothenburg	Heidelberg	Barcelona	Leuven	Maastricht
Gothenburg	-	<0.001	0.11	0.57	0.61
Heidelberg		-	<0.001	<0.001	<0.001
Barcelona			-	0.06	0.24
Leuven				-	0.33
Maastricht					-

Chi squared test p-values between two cohorts

Table 7a. Fibromyalgia / widespread bodily pain

	Gothenburg	Heidelberg	Barcelona	Leuven	Maastricht	p
No fibromyalgia	549 (94%)	251 (92%)	156 (98%)	412 (92%)	410 (82%)	<0.001
Fibromyalgia	32 (6%)	23 (8%)	4 (3%)	38 (8%)	90 (18%)	

Number (percentage) of patients with or without fibromyalgia in the different cohorts, and the overall Fisher's exact test p-value.

Table 7b. Fibromyalgia / widespread bodily pain prevalence between groups.

	Gothenburg	Heidelberg	Barcelona	Leuven	Maastricht
Gothenburg	-	0.13	0.15	0.08	<0.001
Heidelberg		-	0.01	1.00	<0.001
Barcelona			-	0.01	<0.001
Leuven				-	<0.001
Maastricht					-

Fisher's exact test p-values between two cohorts

Table 8a. Chronic or severe fatigue

	Gothenburg	Heidelberg	Barcelona	Leuven	Maastricht	p
No CFS	292 (50%)	140 (49%)	159 (99%)	235 (53%)	333 (67%)	<0.001
CFS	290 (50%)	148 (51%)	1 (1%)	212 (47%)	167 (33%)	

Number (percentage) of patients with or without CFS in the different cohorts, and the overall Fisher's exact test p-value.

Table 8b. Chronic or severe fatigue between groups

	Gothenburg	Heidelberg	Barcelona	Leuven	Maastricht
Gothenburg	-	0.67	<0.001	0.45	<0.001
Heidelberg		-	<0.001	0.33	<0.001
Barcelona			-	<0.001	<0.001
Leuven				-	<0.001
Maastricht					-

Fisher's exact test p-values between two cohorts

Table 9.a Gender distribution between groups based on number of comorbidities in merged cohort

	0 comorbidities	1 comorbidities	2 comorbidities	3-4 comorbidities	p
Female	546 (70%)	405 (78%)	223 (76%)	285 (80%)	<0.001
Male	234 (30%)	116 (22%)	70 (24%)	73 (20%)	

Chi squared test

Table 9b. Comparison of comorbidity groups (Gender)

	0 comorbidities	1 comorbidities	2 comorbidities	3-4 comorbidities
0 comorbidities	-	0.003	0.06	<0.001
1 comorbidities		-	0.66	0.56
2 comorbidities			-	0.33
3-4 comorbidities				-

Chi squared between two numbers of comorbidities

Table 10a. Age distribution between groups based on number of comorbidities in merged cohort

Number of comorbidities	Age (median, IQR)	p-value
0	40 [28-55]	
1	34 [26-47]	<0.001
2	38 [27-50]	
3-4	36 [26-47]	

Kruskal-Wallis test

Table 10b. Comparison of comorbidity groups (Age)

	0 comorbidities	1 comorbidities	2 comorbidities	3-4 comorbidities
0 comorbidities	-	<0.001	0.06	<0.001
1 comorbidities		-	0.054	0.75
2 comorbidities			-	0.08
3-4 comorbidities				-

Mann-Whitney U test adjusted for multiple comparison by False discovery rate correction

Table 11a. Age vs anxiety or depression merged cohort

	No anxiety or depression	Anxiety or depression	p-value
Age (median, IQR)	38 [28-53]	36 [27-48]	<0.001

Mann-Whitney U test

Table 11b. Gender vs anxiety or depression

	No anxiety or depression	Anxiety or depression	p-value
Female (N, %)	938 (54%)	793 (46%)	0.01
Male(N, %)	366 (60%)	243 (40%)	

Chi squared

Table 11c. Age vs fibromyalgia

	No fibromyalgia	Fibromyalgia	p-value
Age (median, IQR)	37 [27-50]	41 [28-51]	0.25

Mann-Whitney U test

Table 11d. Gender vs fibromyalgia

	No fibromyalgia	Fibromyalgia	p-value
Female (N, %)	1307 (89%)	158 (11%)	0.01
Male(N, %)	468 (94%)	29 (6%)	

Chi squared

Table 11e. Age vs fatigue

	No fatigue	Fatigue	p-value
Age (median, IQR)	39 [28-54]	35 [26-47]	<0.001

Mann-Whitney U test

Table 11f. Gender vs fatigue

	No fatigue	Fatigue	p-value
Female (N, %)	825 (56%)	648 (44%)	<0.001
Male(N, %)	334 (67%)	167 (33%)	

Chi squared

Table 12a. Quality of life in patients with/without psychological distress

	No anxiety or depression	Anxiety or depression	p
Barcelona	-	-	
Gothenburg	0.40 (0.84)	-0.41 (0.98)	<0.001
Heidelberg	0.59 (0.83)	-0.62 (0.76)	<0.001
Leuven	0.25 (0.88)	-0.55 (1.02)	<0.001
Maastricht	0.45 (0.85)	-0.60 (0.87)	<0.001
Heidelberg & Maastricht	0.50 (0.84)	-0.61 (0.83)	<0.001
Merged cohort	0.40 (0.86)	-0.50 (0.94)	<0.001

Mean (sd). Differences between groups: t-test

Table 12b. Quality of life in patients with/without fibromyalgia

	No fibromyalgia	Fibromyalgia	p
Gothenburg	-0.03 (0.97)	-0.95 (0.94)	<0.001
Heidelberg	0.07 (0.97)	-0.94 (0.66)	<0.001
Leuven	0.05 (0.97)	-0.58 (1.17)	0.002
Maastricht	0.22(0.92)	-1.00 (0.68)	<0.001
Heidelberg & Maastricht	0.16(0.94)	-0.99 (0.67)	<0.001
Merged cohort	0.07(0.96)	-0.90(0.86)	<0.001

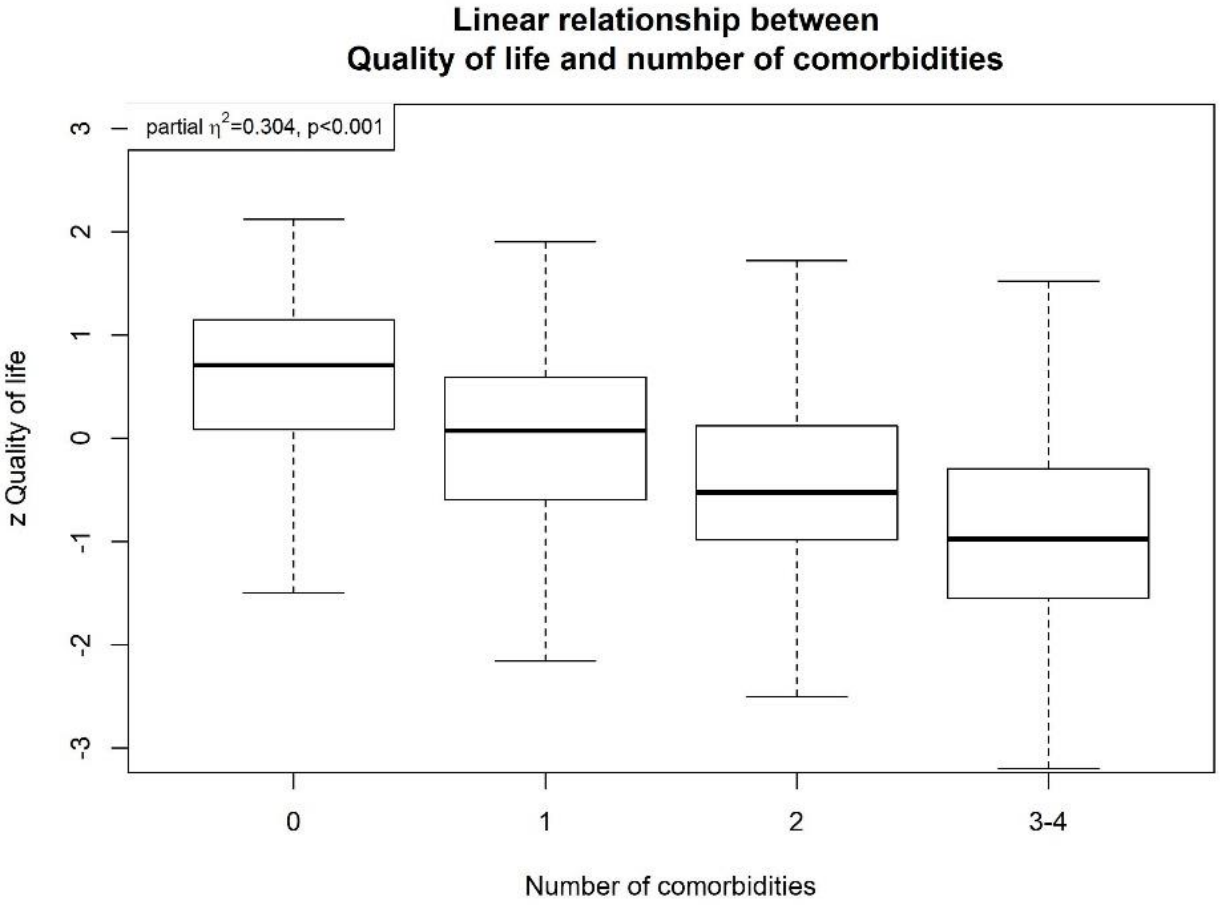
Mean (sd). Differences between groups: t-test

Table 12c. Quality of life in patients with/without chronic fatigue

	No comorbidities	Chronic fatigue	p
Barcelona	-	-	
Gothenburg	-0.03(0.97)	-0.95 (0.94)	<0.001
Heidelberg	0.07 (0.97)	-0.94 (0.66)	<0.001
Leuven	0.05 (0.97)	-0.58 (1.17)	0.002
Maastricht	0.22 (0.92)	-1.00 (0.68)	<0.001
Merged cohort	0.07 (0.96)	-0.90 (0.86)	<0.001

Mean (sd). Differences between groups: t-test

Figure 2.



Median [IQR] and range for the ”number of comorbidity”-groups.

Apprendix 2 06/20/2021

Project title: Development, dIagnostic and prevention of Gender-related Somatic and mental COmorbitiEs in iRritable bowel syndrome In Europe

Academic support/Sponsor: EU, Horizon 2020 Call: H2020-SC1-BHC-2018-2020, „Better Health and care, economic growth and sustainable health systems", DISCOvERIE projekt (SEP-210574985)

Study site: Semmelweis University Department of Psychiatry and Psychotherapy, Budapest

Hungarian database analyses for Work Package 2 (WP 2 Title: „Case-control recruitment and follow up")

Prepared by Pál Czobor PhD. and István Bitter MD, Dsc

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EXECUTIVE SUMMARY

The principal objective of this full-population-based data analyses was to investigate the electronic Hungarian National database in order to delineate the epidemiological records of patients with IBS and its comorbidities. This document provides an excutive summary of the descriptive statistical results of the analyses conducted so far for the project. Detailed information with respect to demographic information and one-dimensional marginal frequency distributions of the variables included in the analyses are provided in Appendix 1. Appendix 2 provides preliminary analyses of associations based on cross-tabulations (2-, 3- or 4-level cross-frequency measures) between demographic characteristics, diagnostic categories and use of medications.

STUDY SETTING AND DATABASE

Hungary has a population of approximately 10 million inhabitants with a centralized healthcare system, with one state-supported payer that funds and documents healthcare related events for the full population. Access to full-scale healthcare information for research purposes is guaranteed by law, and data management and analysis is supported by the help of the Department of Strategic Analysis of National Health Insurance Fund Administration (NHIF). The current analysis was performed as part of WP2 of the DISCOvERIE projekt (SEP-210574985) (“Better Health and care, economic growth and sustainable health systems”) sponsored by the European Union (Horizon 2020 Call: H2020-SC1-BHC-2018-2020) in collaboration with the National Health Insurance Fund Administration (NHIF), and participating personnel at the Semmelweis University Department of Psychiatry and Psychotherapy.

TIME PERIOD OF THE CURRENT INTERIM ANALYSIS

The worldwide coronavirus outbreak and the resulting restrictions from March 2020 caused
a considerable delay in the approval (e.g., ethical permission) and implementation of the current analyses. Once the ethical approval was granted and the database research has restarted at the National Health Insurance Fund Administration, the first data for the project were obtained and the preliminary descriptive analyses were performed based on year 2019, the most recent year before the coronavirus outbreak.

SPECIFIC AIMS

The aim of the current analysis was to obtain preliminary population-based descriptive data about the proportion of the joint occurrence and association of potentially relevant Iritable Bowel Syndrome (IBS) -related gastro-intestinal and psychiatric diagnoses. In order to delineate gender-related comorbidities with affective and anxiety disorders, the current descriptive analyses also examined these associations as a function gender. Additionally, since the prevalence of IBS-related GI conditions and affective and anxiety disorders vary as a function of age, the analyses were broken down by gender and age. We note that in addition to the diagnostic classifications, the use of anxiolytic, antidepressant, and potentially relevant medications for the treatment of IBS-related conditions was also investigated.

METHODS

Variables

In terms of basic demographic information gender (coded as 1 for male and 2 for females) and age were included in the descriptive analyses. Age was recoded into a categorical variable (age_group), according to the following categories: 18-20 years; 21-40 years; 41-60 years; 61-80 years; and 81-99 years. Individuals below 18 and above 99 years were

not included in the current analyses. The list of potentially relevant diagnoses (i.e., GI diagnoses potentially related to IBS, and depressive disorders and anxiety, respectively) and medications are included in Table 1 (see below).

Table 1. GI and mental disorder diagnoses and medications included in the study.

ICD 10 Code	**Diagnostic Category**
E73	lactose intolerance
E74	glucose intolerance
F20	schizophrenia
F32	depressive episode
F33	recurrent depressive disorder
F34	Persistent mood [affective] disorders
F38	other mood [affective] disorders
F39	unspecified mood [affective] disorder
F40	phobic anxiety disorders
F41	other anxiety disorders
F43	reaction to severe stress, and adjustment disorders
F45	somatoform disorders
K30	dyspepsia
K50	Crohn disease
K51	Colitis ulcerosa
K52	Other noninfective gastroenteritis and colitis
K57	Diverticular disease of intestine
K5800	Irritable bowel syndrome
K5890	Irritable bowel syndrome without diarrhea
K5900	constipation
K5910	functional diarrhea
K9150	postcholecystectomy syndrome
R10	abdominal and pelvic pain
R14	flatulence

R1950	other faecal abnormalities
ATC Code	**ATC descriptor**
C10AC01	cholestyramine
A03AA04	duspatalin
A03AD02	no-spa
A03AX04	dicetel
A03AX08	meteospasmyl
A04AA01	ondansetron
A06AB02	bisacodyl
A06AD15	macrogol
A06AX05	resolor
A07AA11	normix
A07DA03	loperamid
N05B	anxiolytics
N06AA	non-selective monoamine reuptake inhibitors
N06AB	selective serotonin reuptake inhibitors
N06AG	monoamine oxidase A inhibitors
N06AX	other antidepressants

All patients who had a health record for hospital or ambulatory care in the national database were included in the analyses. Each of the rows in Table 1 (diagnostic codes or medications) denotes one (original source) variable in the analysis database; these variables were represented in a binary form (1/0; e.g., for anxyiolytics, 1 means that a patients had a reimbursement of the anxiolytic medication during the given year, i.e. an outpatient filled a prescription in a pharmacy). Based on the data protection rules in Hungary, which aim to prevent potential de-identification of sensitive health information, for the purpose of cross-tabulations the above mentioned original source variables were aggregated into broader categories for the analyses. Such broad variable categories included the following binary variables, described in Table 2 below.

Table 2. Derived variables used in the descriptive statistical analyses.

Derived variable name	**Descriptor**
affective	binary variable 1/0; 1=any diagnosis in affective disorder categories including F33, F34, F38, F39
anxiety	binary variable 1/0; 1=any diagnosis in affective disorder categories including F40 and F41
med_depr	1/0; 1=any use of anti-depressant meds in the ATC categories of N06AB, N06AG, N06AX
med_anx	binary variable 1/0; 1= 1=any use of anxiolytic meds in the ATC category of N05B
affective_expand	binary variable 1/0; 1= any affective diagnosis or any anti-depressant use in the above categories
anxiety_expand	binary variable 1/0; 1= any anxiety diagnosis or any anxiolytic use in the above categories
IBSnarrow	binary variable 1/0; 1=any diagnosis in the K5800 or K5890 category
Any_GI	binary variable 1/0; 1= any diagnosis in the following Gastro-Intestinal (GI) disorder categories: E73, E74, K30, K50, K51, K52, K57, K5800, K5890, K5900, K5910, K9150, R10, R14, R1950.

Statistical analyses

The statistical analyses were based on descriptive statistical measures, including absolute and relative frequency indices such as counts and percentages. Associations were examined through 2-, 3- or 4-level cross-frequency measures (cross-tabulations, e.g., a 4-level frequency table for Gender x Age x IBS (yes/no) x Affective disorders (yes/no)).

RESULTS

Descriptive demographic data

sample,

A total of 1,747,695 individuals had a health record for hospital or ambulatory care in the national database in 2019 and were included in the analyses. In terms of gender proportions, the sample had an approximately 1:2 ratio of male (32.7%) to female (67.3%) proportion. In terms of age distributions, individuals in the age group of 61-80 years had the highest proportion in the sample. Specifically, the proportion of individuals in the 18-20, 21-40, 41-60 and 61-80, and 81-99 year age group was 1.5%, 15%, 29.8% 41.8% and 11.9%, respectively. The gender distribution in the sample across age groups showed only a relatively small variation up until the highest age group (where the proportion of females increased). In particular, the proportion of females in the 18-20, 21-40, 41-60 and 61-80 and 81-99 year age groups were 65.1%, 61.3%, 63.8%, 69.0% and 78.1%, respectively.

Diagnostic distribution and use of medications

The proportion of individuals with the aforementioned broader diagnostic categories for depression and anxiety were 8.5% and 10.5% respectively. A total of 27.8% of the included sample had a GI diagnosis according to the broad diagnostic category described in Table 2. The proportion of patients in the more restricted IBS category that included the diagnoses of K5800 and K5890 was 0.6%. The proportion of patients who used antidepressant or anxiolytic medications was 21.6% and 60.6% in the samples, respectively. The proportion of patients who used any medication in the broader category of GI medications (see Table 2 for details) deemed potentially relevant to the IBS-related conditions was 11.3%.

Affective and anxiety disorders in patients as a function of IBS condition

Cross-tabulation of the absence and presence of the more narrowly defined IBS condition with affective (see Table3a below) and anxiety diagnoses (Table 3b, below) indicated a lower proportion of these diagnoses for patients who presented with the IBS condition. For example, among patients who presented with IBS, the proportion with affective diagnosis was 6.7% as compared to 8.5% who did not have this condition. As shown by Tables 3c and 3d (below), the results were similar for the more broadly defined IBS related GI category (any_GI): the proportion of affective and anxiety diagnoses was higher for patients who did not have this condition.

Table 3a. Narrowly defined IBS category (IBSnarrow) vs. presence of affective disorders.

Crosstab

			affective		
			,00	1,00	Total
IBSnarrow	,00	Count	1589192	147803	1736995
		% within IBSnarrow	91,5%	8,5%	100,0%
		% within affective	99,4%	99,5%	99,4%
		% of Total	90,9%	8,5%	99,4%
	1,00	Count	9986	714	10700
		% within IBSnarrow	93,3%	6,7%	100,0%
		% within affective	0,6%	0,5%	0,6%
		% of Total	0,6%	0,0%	0,6%

Table 3b. Narrowly defined IBS category (IBSnarrow) vs. presence of anxiety disorders

Crosstab

			anxiety		
			,00	1,00	Total
IBSnarrow	,00	Count	1554465	182530	1736995
		% within IBSnarrow	89,5%	10,5%	100,0%
		% within anxiety	99,4%	99,5%	99,4%
		% of Total	88,9%	10,4%	99,4%
	1,00	Count	9863	837	10700
		% within IBSnarrow	92,2%	7,8%	100,0%
		% within anxiety	0,6%	0,5%	0,6%

	% of Total	0,6%	0,0%	0,6%

Table 3c. Broadly defined IBS related GI category (any_GI) vs. affective disorders

Crosstab

			affective		
			,00	1,00	Total
any_GI	,00	Count	1132941	128441	1261382
		% within any_GI	89,8%	10,2%	100,0%
		% within affective	70,8%	86,5%	72,2%
		% of Total	64,8%	7,3%	72,2%
	1,00	Count	466237	20076	486313
		% within any_GI	95,9%	4,1%	100,0%
		% within affective	29,2%	13,5%	27,8%
		% of Total	26,7%	1,1%	27,8%

Table 3d. Broadly defined IBS related GI category (any_GI) vs. anxiety disorders

Crosstab

			anxiety		
			,00	1,00	Total
any_GI	,00	Count	1103020	158362	1261382
		% within any_GI	87,4%	12,6%	100,0%
		% within anxiety	70,5%	86,4%	72,2%
		% of Total	63,1%	9,1%	72,2%
	1,00	Count	461308	25005	486313
		% within any_GI	94,9%	5,1%	100,0%
		% within anxiety	29,5%	13,6%	27,8%
		% of Total	26,4%	1,4%	27,8%

Analyses by gender: Affective and anxiety disorders in patients as a function of IBS condition in males and females

A separate cross-tabulation by gender of the absence and presence of the more narrowly defined IBS condition with affective (see Table4a) and anxiety diagnoses (Table 4 b) indicated that a lower proportion of these diagnoses in patients who presented with the IBS condition occurs both in males and females. Nevertheless, it is noteworthy that the proportion of patients with affective or anxiety diagnoses is disproportionately higher in females than in males when the IBS condition is present. For example, when the IBS condition is met, the proportion of affective disorders is 7.9% and 4.3% for females and males, respectively; the analogous numbers for females and males were 9.3% and 6.8% for patients without the IBS condition, indicating markedly more balanced distribution in this group.

Table 4a. Analysis by gender: Narrowly defined IBS category (IBSnarrow) vs. presence of affective disorders in males and females.

Crosstab

Gender				affective ,00	affective 1,00	Total
1	IBSnarrow	,00	Count	528984	38540	567524
			% within IBSnarrow	93,2%	6,8%	100,0%
			% within affective	99,4%	99,6%	99,4%
			% of Total	92,6%	6,7%	99,4%
		1,00	Count	3397	151	3548
			% within IBSnarrow	95,7%	4,3%	100,0%
			% within affective	0,6%	0,4%	0,6%
			% of Total	0,6%	0,0%	0,6%
2	IBSnarrow	,00	Count	1060208	109263	1169471
			% within IBSnarrow	90,7%	9,3%	100,0%
			% within affective	99,4%	99,5%	99,4%
			% of Total	90,1%	9,3%	99,4%
		1,00	Count	6589	563	7152
			% within IBSnarrow	92,1%	7,9%	100,0%
			% within affective	0,6%	0,5%	0,6%
			% of Total	0,6%	0,0%	0,6%

Table 4b. Analysis by gender: Narrowly defined IBS category (IBSnarrow) vs. presence of anxiety disorders in males and females

Crosstab

Gender				anxiety ,00	anxiety 1,00	Total
1	IBSnarrow	,00	Count	511725	55799	567524
			% within IBSnarrow	90,2%	9,8%	100,0%
			% within anxiety	99,3%	99,7%	99,4%
			% of Total	89,6%	9,8%	99,4%
		1,00	Count	3370	178	3548
			% within IBSnarrow	95,0%	5,0%	100,0%
			% within anxiety	0,7%	0,3%	0,6%
			% of Total	0,6%	0,0%	0,6%
2	IBSnarrow	,00	Count	1042740	126731	1169471
			% within IBSnarrow	89,2%	10,8%	100,0%
			% within anxiety	99,4%	99,5%	99,4%
			% of Total	88,6%	10,8%	99,4%
		1,00	Count	6493	659	7152
			% within IBSnarrow	90,8%	9,2%	100,0%
			% within anxiety	0,6%	0,5%	0,6%
			% of Total	0,6%	0,1%	0,6%

Analyses by age group and gender: Affective and anxiety disorders in patients as a function of IBS condition and age in males and females

Results of the analysis of the diagnostic associations simultaneously by age group and gender are presented respectively for the affective and anxiety diagnoses in Table 5a and Table 5b. As shown by the cross-tabulation data displayed in these tables, the lower proportion of affective and anxiety diagnoses in patients who presented with the IBS condition is observable across all age groups both for males and females, with one exception. Specifically, in the lowest age group (18-20 years) in males, the above mentioned proportion shows a reversal (i.e., higher proportion of affective and anxiety comorbidities are present when the IBS condition is present). Additionally, starting from the age group of 21-40 years, the proportion of patients with affective or anxiety diagnoses

is disproportionately higher in females than in males when the IBS condition is present as compared to patients without the IBS condition, indicating a markedly higher gender imbalance in the former group.

Table 5a. Analysis by age group and gender: Narrowly defined IBS category (IBSnarrow) vs. presence of affective disorders in males and females

Crosstab

					affective		
age_group	gender				,00	1,00	Total
18-20	1	IBSnarrow	,00	Count	8594	373	8967
				% within IBSnarrow	95,8%	4,2%	100,0%
				% within affective	99,2%	98,7%	99,2%
				% of Total	95,1%	4,1%	99,2%
			1,00	Count	68	5	73
				% within IBSnarrow	93,2%	6,8%	100,0%
				% within affective	0,8%	1,3%	0,8%
				% of Total	0,8%	0,1%	0,8%
	2	IBSnarrow	,00	Count	15955	751	16706
				% within IBSnarrow	95,5%	4,5%	100,0%
				% within affective	99,2%	99,5%	99,2%
				% of Total	94,8%	4,5%	99,2%
			1,00	Count	126	4	130
				% within IBSnarrow	96,9%	3,1%	100,0%
				% within affective	0,8%	0,5%	0,8%
				% of Total	0,7%	0,0%	0,8%
21-40	1	IBSnarrow	,00	Count	95267	5368	100635
				% within IBSnarrow	94,7%	5,3%	100,0%
				% within affective	99,0%	99,6%	99,1%
				% of Total	93,8%	5,3%	99,1%
			1,00	Count	945	20	965
				% within IBSnarrow	97,9%	2,1%	100,0%
				% within affective	1,0%	0,4%	0,9%
				% of Total	0,9%	0,0%	0,9%
	2	IBSnarrow	,00	Count	150727	8316	159043
				% within IBSnarrow	94,8%	5,2%	100,0%
				% within affective	98,9%	99,5%	98,9%
				% of Total	93,7%	5,2%	98,9%

			1,00	Count	1725	38	1763
				% within IBSnarrow	97,8%	2,2%	100,0%
				% within affective	1,1%	0,5%	1,1%
				% of Total	1,1%	0,0%	1,1%
41-60	1	IBSnarrow	,00	Count	172316	14594	186910
				% within IBSnarrow	92,2%	7,8%	100,0%
				% within affective	99,3%	99,6%	99,3%
				% of Total	91,6%	7,8%	99,3%
			1,00	Count	1241	60	1301
				% within IBSnarrow	95,4%	4,6%	100,0%
				% within affective	0,7%	0,4%	0,7%
				% of Total	0,7%	0,0%	0,7%
	2	IBSnarrow	,00	Count	293548	36214	329762
				% within IBSnarrow	89,0%	11,0%	100,0%
				% within affective	99,3%	99,5%	99,3%
				% of Total	88,4%	10,9%	99,3%
			1,00	Count	2139	187	2326
				% within IBSnarrow	92,0%	8,0%	100,0%
				% within affective	0,7%	0,5%	0,7%
				% of Total	0,6%	0,1%	0,7%
61-80	1	IBSnarrow	,00	Count	209527	16042	225569
				% within IBSnarrow	92,9%	7,1%	100,0%
				% within affective	99,5%	99,6%	99,5%
				% of Total	92,4%	7,1%	99,5%
			1,00	Count	1025	57	1082
				% within IBSnarrow	94,7%	5,3%	100,0%
				% within affective	0,5%	0,4%	0,5%
				% of Total	0,5%	0,0%	0,5%
	2	IBSnarrow	,00	Count	448265	53811	502076
				% within IBSnarrow	89,3%	10,7%	100,0%
				% within affective	99,5%	99,5%	99,5%
				% of Total	88,8%	10,7%	99,5%
			1,00	Count	2300	293	2593
				% within IBSnarrow	88,7%	11,3%	100,0%
				% within affective	0,5%	0,5%	0,5%
				% of Total	0,5%	0,1%	0,5%
81-99	1	IBSnarrow	,00	Count	43280	2163	45443
				% within IBSnarrow	95,2%	4,8%	100,0%

				% within affective	99,7%	99,6%	99,7%
				% of Total	95,0%	4,7%	99,7%
			1,00	Count	118	9	127
				% within IBSnarrow	92,9%	7,1%	100,0%
				% within affective	0,3%	0,4%	0,3%
				% of Total	0,3%	0,0%	0,3%
	2	IBSnarrow	,00	Count	151713	10171	161884
				% within IBSnarrow	93,7%	6,3%	100,0%
				% within affective	99,8%	99,6%	99,8%
				% of Total	93,5%	6,3%	99,8%
			1,00	Count	299	41	340
				% within IBSnarrow	87,9%	12,1%	100,0%
				% within affective	0,2%	0,4%	0,2%
				% of Total	0,2%	0,0%	0,2%

Table 5b. Analysis by age group and gender: Narrowly defined IBS category (IBSnarrow) vs. presence of affective disorders in males and females

Crosstab

					anxiety		
age_group	gender				,00	1,00	Total
18-20	1	IBSnarrow	,00	Count	7969	998	8967
				% within IBSnarrow	88,9%	11,1%	100,0%
				% within anxiety	99,1%	99,6%	99,2%
				% of Total	88,2%	11,0%	99,2%
			1,00	Count	69	4	73
				% within IBSnarrow	94,5%	5,5%	100,0%
				% within anxiety	0,9%	0,4%	0,8%
				% of Total	0,8%	0,0%	0,8%
	2	IBSnarrow	,00	Count	14961	1745	16706
				% within IBSnarrow	89,6%	10,4%	100,0%
				% within anxiety	99,2%	99,5%	99,2%
				% of Total	88,9%	10,4%	99,2%
			1,00	Count	121	9	130
				% within IBSnarrow	93,1%	6,9%	100,0%
				% within anxiety	0,8%	0,5%	0,8%
				% of Total	0,7%	0,1%	0,8%
21-40	1	IBSnarrow	,00	Count	86577	14058	100635
				% within IBSnarrow	86,0%	14,0%	100,0%

				% within anxiety	99,0%	99,7%	99,1%
				% of Total	85,2%	13,8%	99,1%
			1,00	Count	917	48	965
				% within IBSnarrow	95,0%	5,0%	100,0%
				% within anxiety	1,0%	0,3%	0,9%
				% of Total	0,9%	0,0%	0,9%
	2	IBSnarrow	,00	Count	139328	19715	159043
				% within IBSnarrow	87,6%	12,4%	100,0%
				% within anxiety	98,8%	99,4%	98,9%
				% of Total	86,6%	12,3%	98,9%
			1,00	Count	1647	116	1763
				% within IBSnarrow	93,4%	6,6%	100,0%
				% within anxiety	1,2%	0,6%	1,1%
				% of Total	1,0%	0,1%	1,1%
41-60	1	IBSnarrow	,00	Count	165160	21750	186910
				% within IBSnarrow	88,4%	11,6%	100,0%
				% within anxiety	99,3%	99,7%	99,3%
				% of Total	87,8%	11,6%	99,3%
			1,00	Count	1230	71	1301
				% within IBSnarrow	94,5%	5,5%	100,0%
				% within anxiety	0,7%	0,3%	0,7%
				% of Total	0,7%	0,0%	0,7%
				% of Total	88,4%	11,6%	100,0%
	2	IBSnarrow	,00	Count	284642	45120	329762
				% within IBSnarrow	86,3%	13,7%	100,0%
				% within anxiety	99,3%	99,5%	99,3%
				% of Total	85,7%	13,6%	99,3%
			1,00	Count	2108	218	2326
				% within IBSnarrow	90,6%	9,4%	100,0%
				% within anxiety	0,7%	0,5%	0,7%
				% of Total	0,6%	0,1%	0,7%
61-80	1	IBSnarrow	,00	Count	208866	16703	225569
				% within IBSnarrow	92,6%	7,4%	100,0%
				% within anxiety	99,5%	99,7%	99,5%
				% of Total	92,2%	7,4%	99,5%
			1,00	Count	1035	47	1082
				% within IBSnarrow	95,7%	4,3%	100,0%
				% within anxiety	0,5%	0,3%	0,5%

				% of Total	0,5%	0,0%	0,5%
	2	IBSnarrow	,00	Count	452480	49596	502076
				% within IBSnarrow	90,1%	9,9%	100,0%
				% within anxiety	99,5%	99,4%	99,5%
				% of Total	89,7%	9,8%	99,5%
			1,00	Count	2315	278	2593
				% within IBSnarrow	89,3%	10,7%	100,0%
				% within anxiety	0,5%	0,6%	0,5%
				% of Total	0,5%	0,1%	0,5%
81-99	1	IBSnarrow	,00	Count	43153	2290	45443
				% within IBSnarrow	95,0%	5,0%	100,0%
				% within anxiety	99,7%	99,7%	99,7%
				% of Total	94,7%	5,0%	99,7%
			1,00	Count	119	8	127
				% within IBSnarrow	93,7%	6,3%	100,0%
				% within anxiety	0,3%	0,3%	0,3%
				% of Total	0,3%	0,0%	0,3%
		Total		Count	43272	2298	45570
				% within IBSnarrow	95,0%	5,0%	100,0%
				% within anxiety	100,0%	100,0%	100,0%
				% of Total	95,0%	5,0%	100,0%
	2	IBSnarrow	,00	Count	151329	10555	161884
				% within IBSnarrow	93,5%	6,5%	100,0%
				% within anxiety	99,8%	99,6%	99,8%
				% of Total	93,3%	6,5%	99,8%
			1,00	Count	302	38	340
				% within IBSnarrow	88,8%	11,2%	100,0%
				% within anxiety	0,2%	0,4%	0,2%
				% of Total	0,2%	0,0%	0,2%
	Total	IBSnarrow	,00	Count	194482	12845	207327
				% within IBSnarrow	93,8%	6,2%	100,0%
				% within anxiety	99,8%	99,6%	99,8%
				% of Total	93,6%	6,2%	99,8%
			1,00	Count	421	46	467
				% within IBSnarrow	90,1%	9,9%	100,0%
				% within anxiety	0,2%	0,4%	0,2%
				% of Total	0,2%	0,0%	0,2%
				% within anxiety	100,0%	100,0%	100,0%

			% of Total	90,2%	9,8%	100,0%
	2	IBSnarrow	,00	Count	1042740	126731	1169471
				% within IBSnarrow	89,2%	10,8%	100,0%
				% within anxiety	99,4%	99,5%	99,4%
				% of Total	88,6%	10,8%	99,4%
			1,00	Count	6493	659	7152
				% within IBSnarrow	90,8%	9,2%	100,0%
				% within anxiety	0,6%	0,5%	0,6%
				% of Total	0,6%	0,1%	0,6%

CONCLUSIONS

Cross-tabulation of the absence and presence of the IBS-related conditions (IBS diagnosis based on a narrow definition, and a category of more broadly defined IBS-related conditions) with affective and anxiety diagnoses indicated a lower proportion of these diagnoses for patients who presented with the IBS condition. These overall associations were also observable for the more broadly defined categories of affective and anxiety disorders, which included patients who received these medications (but did not receive a formal diagnosis of the respective mental disorders). These associations were detected both in males and females and were generally observable across most of the age groups. Additionally, starting from the age group of 21-40 years, the proportion of patients with affective or anxiety diagnoses is disproportionately higher in females than in males when the IBS condition is present as compared to patients without the IBS condition, indicating a markedly higher gender imbalance in the former group. These findings highlight the importance of further delineating the differential gender related associations between the Irritable Bowel Syndrome and psychiatric conditions, including affective symptoms and anxiety.

The fact that the presence of IBS-related conditions was associated with a lower proportion of affective and anxiety diagnoses in patients who presented with the IBS condition suggests that the affective and anxiety disorders remain undetected and are severely undiagnosed in this patient population in Hungary. This is consistent with the

result of a comprehensive survey (stated in execute summary in [1-2]) that shows that the incidence and prevalence of many gastrointestinal disorders is under-reported in many eastern European countries when compared with other regions of Europe. Additionally, this is also consistent with the results of a large study from Finland that concluded that " Seeking health care for abdominal complaints is associated with abdominal symptoms rather than psychiatric comorbidity." [3] The authors of this study also emphasized that "Depression and somatic non-GI symptoms possibly predict health-care seeking for non-GI reasons simply because they belong to the list of many other non-GI reasons for consulting a doctor." Nonetheless, the results of the current interim analyses should be considered as descriptive and preliminary. Our further population-based analyses will examine a longer time period and will study patient pathways to explore potential causal associations and outcomes (e.g., mortality), and include matched healthy controls for the latter analyses.

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